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EXAMINER	
ZISKA, S	
ART UNIT	**PAPER NUMBER**
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1804
DATE MAILED:
04/25/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on March 16, 1995 March 29, 1995 March 31, 1995 March 23, 1995 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), zero (0) days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☒ Telephone Interview Summary paper no. 19, 5/24/95

Part II SUMMARY OF ACTION

1. ☒ Claims 26, 27, 32-44, 46-66, 69, 70, 73-75, 77-82, 84-88, 91, 92, 94-98, 100, 102-104 & 105 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-25, 28-31, 45, 67, 71, 72, 76, 83, 89, 90, 93, 99 and 101 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 26, 27, 32-44, 46-66, 69, 70, 73-75, 77-82, 84-88, 91, 92, 94-98, 100, 102-105 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

This Office Action is issued in response to Applicant's petition to the Group Director, paper no. 21, submitted March 16, 1995, and to the supplemental communication to the Group Director, paper no. 22, submitted March 23, 1995, directing the Examiner to withdraw the previous Final Office Action, paper no. 18, mailed March 10, 1993. This Office Action is further in response to the communication to the Group Director, paper no. 24, submitted March 29, 1995, transmitting the recent In re Deuel decision. The Group Director, pursuant to the provisions of 37 CFR 1.181., 1.182 and/or 1.183, has directed the Examiner to withdraw finality only, to enter and examine the claim faxed March 31, 1995, and to consider the petition as a request for reconsideration.

The newly added claim has been entered and numbered as claim 105 under Rule 126. Claims 1-25, 28-31, 45, 67, 71, 72, 76, 83, 89, 90, 93, 99 and 101 have been cancelled; claims 26, 27, 32-44, 46-66, 69, 70, 73-75, 77-82, 84-88, 91, 92, 94-98, 100, 102-104 and 105 are active and examined in this Office Action.

The declaration of Dr. Liskay is acknowledged, has been considered and is addressed, below.

It is noted for the record that the amendment to claim 100 was not entered due to inconsistencies between claim 100 as amended in amendment B and amendment C. Therefore, claim 100 stands as in amendment B, paper no. 8 of June 1, 1994.

The rejection of claims 26, 27, 32-44, 46-66, 69, 70, 73-75, 77-82, 84-88, 91, 92, 94-98, 100, 102-104 under 35 U.S.C. 112, first paragraph, regarding the integration of the amplifiable gene within the endogenous gene is withdrawn. However, the amendments to the claims regarding the phrase "endogenous target gene coding sequence is not disrupted" constitutes new matter and therefore the amendments to the claims has necessitated a new ground of rejection:

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification as originally filed, does not provide support for the invention as is now claimed. The phrase "endogenous target gene coding sequence is not disrupted" constitutes new matter since there is no support in the specification for the newly added negative limitation. Applicant's attention is directed to specification page 3, lines 12-17, wherein the use of homologous recombination for "integration of an amplifiable gene and other regulatory sequences in proximity to a gene of interest without interruption of the production of a proper transcript" is not commensurate in scope with the newly added negative claim limitation of "so that the endogenous target gene coding sequence is not disrupted". Although the phrase "a proper transcript" is undefined, integration into the target gene coding sequence does not inhibit the production of a proper transcript since integration into the coding region will not inhibit transcription. A "proper transcript" is not known in the art to be commensurate in scope with an uninterrupted coding sequence.

Claims 26, 27, 32-44, 46-66, 69, 70, 73-75, 77-82, 84-88, 91, 92, 94-98, 100, 102-104 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention as claimed, i.e., failing to provide an enabling disclosure. The specification discloses use of amplifiable genes which are useful in amplification of an operatively linked gene when linked 5'to the gene of interest. The specification fails to disclose use of amplifiable genes linked 3' to, or within, the endogenous target gene. Further, the specification fails to provide any evidence that the well known amplifiable genes exemplified in Ringold would enable amplification of the operatively associated gene when integrated any where else other than 5' to the target endogenous gene. The examiner is unaware of any art teaching that, for example, the DHFR gene integrated 3' of or into the target gene would result in amplification of the target gene. Case law teaches (Ex parte Forman, 230 USPQ 546, 547 (PTO Bd. App. Int. 1986)that "the disclosure of a patent application must enable practice of the invention claimed without undue experimentation", wherein factors involved in the determination of undue experimentation were deemed to include "the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims". The specification fails to provide any guidance

or direction of using amplifiable genes integrated into other gene locations and the state of the prior art is such that amplifiable genes are only used in locations 5' to the target gene. In view of the absence of working examples showing amplification of target genes having amplifiable genes integrated within or 3' to first exon and the lack of such examples in the prior art, it would require undue experimentation by one of ordinary skill to practice the invention as claimed since one would have to invent or identify amplifiable genes capable of working from other non-5' positions.

Claims 27, 32-43, 49-61, 63-66, 73, 75, 77-82, 84-88, 91, 92, 94-96, 98-100 and 102-104 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The rejection of claims 27, 32-44, 46-47, 49-61, 63-66, 73, 75, 77-82, 84-88, 91, 98, 100, 102-104 under 35 U.S.C. 112, second paragraph, is maintained for reasons set forth in the previous Office Action. Applicants have not argued the rejection in the petition.

The following rejections under 35 U.S.C. 103 are maintained for reasons of record set forth in the previous Office Action:

the rejection of claims 26, 38-41, 69 and 70 as being unpatentable over Smithies and Nandi taken with Thompson;

the rejection of claims 37 and 42 as being unpatentable over Smithies and Nandi taken with Thompson as applied to claims 26, 38-41, 69 and 70 above and further in view of Palmer;

the rejection of claims 33-36 as being unpatentable over Smithies, Nandi and Thompson as applied to claims 26, 38-41, 69 and 70 above and further in view of Frohman and Thomas;

the rejection of claims 27, 32, 43, 91, 92 and 94 as being unpatentable over Smithies, Nandi and Thompson as applied to

claims 26, 38-41, 69 and 70 above and further in view of Anderson and Ringold;

the rejection of claims 44, 46 and 47 as being patentable over Smithies, Nandi and Thompson as applied to claims 26, 38-41, 69 and 70 above and further in view of Nelson;

the rejection of claims 48, 50, 52-55 and 79 as being unpatentable over Smithies, Nandi taken with Thompson;

the rejection of claims 51 and 56 as being unpatentable over Smithies, Nandi taken with Thompson as applied to claims 48, 50, 52-55 and 79 above and further in view of Palmer;

the rejection of claims 58-61 as being unpatentable over Smithies, Nandi and Thompson as applied to claims 48, 50, 52-55 and 79 above and further in view of Frohman and Thomas;

the rejection of claims 49, 57, 75, 80 and 81 over Smithies, Nandi and Thompson as applied to claims 48, 50, 52-55 and 79 above and further in view of Anderson and Ringold;

the rejection of claims 62, 64-66, 86, 97 and 102 as being unpatentable over Nelson taken with Smithies, Nandi and Thompson;

the rejection of claims 63, 82, 87, 88, 98 and 100 as being unpatentable over Nelson taken with Smithies, Nandi and Thompson as applied to claims 62, 64-66, 86, 97 and 102 above and further in view of Ringold and Anderson;

the rejection of claims 73, 74, 77, 78, 84, 85, 95, 96, 103 and 104 as being unpatentable over Smithies, Nandi, Thompson or Nelson, Smithies, Nandi and Thompson or Smithies, Nandi, Thompson, Nelson, Ringold and Anderson as applied to claims 26, 27, 48, 75, 62, 82, 69, 91, 97, 98 and further in view of Foecking and Boshart.

In the petition, Applicants have argued that the Office Action was improper since the Examiner acted outside the scope of her authority and erroneously issued the Office Action. The issue

has now been rectified as indicated by the signature of the Group Director.

Applicants have argued that the art used by the examiner to support the obviousness rejection under 35 U.S.C. 103 is the very same art that the Applicant has already addressed and has relied on to support non-obviousness of the claimed invention. Applicants have further argued that since the references relied upon by the both sides are the same the different conclusions reached can only be due to different analyses and interpretations of the teachings of the art and that the examiner's analysis and opinion must give way to one truly skilled in the art who was active in the field and "on the scene" at the time the claimed invention was made. However, reference is available as prior art and the combination of references provides a prima facie case of obviousness not overcome by Applicant's arguments. The determination of obviousness requires both a motivation or suggestion to combine the references as well as a reasonable expectation of success and the rejections of the claimed invention clearly set forth both motivation and the reasonable expectation of success. Thompson et al. provide motivation to target changes to the control sequences of genes to increase output of the product and Smithies et al. provide an expectation for success by showing successful recombination.

Applicants have argued that the declaration filed by Dr. Liskay analyzes the factual underpinnings of the obviousness inquiry by putting into context what the articles relied upon by the examiner in the March 6th Office Action would or would not have meant to one of ordinary skill in the art at the time the claimed invention was made. However, while the declaration does state some facts, the declaration is mainly an opinion declaration and given little probative value.

Applicants have argued that ironically, one of the references relied on by the examiner (the Smithies reference) was supplied by the declarant, Dr. Liskay, to show failure in the art and no reasonable expectation of success. However, contrary to applicant's assertions, the Smithies reference does not show "failure" in the art since Smithies discloses successful gene targeting by homologous recombination. Further, the examiner used Smithies to teach exactly what declarant stated Smithies taught and therefore the examiner is in agreement with declarant regarding the teachings of Smithies. Where the examiner differs with the declarant is in his conclusion of the Smithies reference or what applicants refer to as "failure in the art". Applicants have not defined "failure in the art" but to the extent that Smithies teaches gene targeting by homologous recombination, and both applicants and the examiner agree that Smithies does, Smithies does not fail. Therefore, the foregoing represents one example of the differences in the analysis of the references by the examiner and the declarant. Smithies et al. indicate that the frequency of success is at present modest and that the data show unequivocally that the modification of a specific human gene is possible in vivo. See page 230, left column. Thus, one of skill in the art would not view this as a failure but rather as a success. Further, contrary to applicant's arguments regarding the reasonable expectation of success, neither applicants nor declarant has provided any evidence of no reasonable expectation of success. The cited prior art clearly sets forth that any gene may be the target of a successful homologous recombination, that homologous recombination may be used to insert a mutated gene, insert a corrected gene, insert a marker gene into the coding region of a protein, insert mutations in the 5' region, insert mutations into the 3' region, insert regulatory sequences such as translation initiation regions, enhancers, 3' regulatory region.

In short, the prior teaches that homologous recombination may be used to alter a desired nucleotide sequence any place in a gene of interest for any purpose (mutation, correction, experimentation), that expression of the gene product is obtained if the desired product is a protein and that transcription occurs from the desired gene. There is a reasonable expectation of success and applicants have not provided any convincing evidence to the contrary. Contrary to Applicant's assertions, Dr. Liskay has not provided evidence as to why one of ordinary skill in the art at the time the claimed invention was made would not have had a reasonable expectation of success other than his opinion. Therefore, the examiner's determination of obviousness is based upon the motivation and reasonable expectation of success found in the cited prior art and lack of evidence to the contrary provided by any of applicant's arguments, submissions and evidence and arguments in the declaration.

Applicants have further argued that Dr. Liskay analyzes the factual underpinnings of an obviousness inquiry, for example, why the cited art does not suggest the invention and why one of ordinary skill would not have had a reasonable expectation of success. They argue that a legal determination of non-obviousness must follow from his factual analysis citing In re Vaeck and In re Oelrich. With respect to Vaeck, the successful homologous recombination in Smithies et al. would have provided a reasonable expectation of success to those of ordinary skill in the art. In regard to Oelrich, the declaration of Dr. Liskay is not fact based in the manner found persuasive in Oelrich. Moreover, when one conducts the weighing of evidence as suggested in Oelrich, one cannot conclude that Dr. Liskay's declaration outweighs the suggestions provided in the prior art. Contrary to applicant's arguments, Dr. Liskay has not fairly read the Thompson reference

and secondly has not provided evidence as to no reasonable expectation of success.

Applicants have argued that Dr. Liskay is an unbiased researcher who is eminently qualified to set forth what was known and what was not known, expected or unexpected, and that the examiner can not substitute her judgement for that of a qualified expert citing In re Zeidler. In re Zeidler is not controlling here. In that case the declaration gave an analysis of the washfastness, water-solubility and color in a comparison between the invention dye and a reference they considered to be the closest prior art but the instant declaration provides no such evidence. Contrary to applicant's arguments, the examiner has not "substituted her judgement for that of a qualified expert" but merely disagrees with his conclusion and further can point to errors in his "facts". Contrary to applicant's further assertions, the facts of record as set forth by the record support the examiner's conclusion of obviousness in view of the motivation and reasonable expectation of success provided by the cited references.

Applicants have argued that the March 6th Office Action itself indicates that the examiner is, in fact, engaging in an improper obviousness analysis since she is relying on hindsight reconstruction; and that the examiner utilizes applicant's discovery and teaching to support a finding that one of ordinary skill would have had a reasonable expectation of success. However, contrary to such arguments, the examiner has looked to the art for both motivation and expectation of success and found both therein. Thus, no "hindsight reconstruction" has occurred.

Applicants have argued that the examiner's rejection of certain claims under 35 U.S.C. 112, first paragraph, regarding entitlement to priority date is irrelevant to any issue of patentability in this application since there is no intervening

art applied against the claims and that therefore it is improper for the examiner to consider this issue. The rejection under 112, first paragraph, has been withdrawn and "nucleotide regulatory sequences" per se finds support in both this application and its parent. With respect to applicants' arguments to "promoter", the instant claims are not so limited and thus there is no issue to be discussed.

Applicants have argued that regarding claim 27, that integration within the endogenous target gene is actually within the intron, not the coding sequence, and that therefore the claim is not internally inconsistent. However, it is well settled that while claims are to be interpreted in light of the specification, the claims are not limited by the specification and the rejection may be overcome by adding the clarifying limitation that the insertion site is within an intron.

Applicants have argued at page 15 that an interference should be declared. However, and as previously set forth, an interference cannot be declared until the claims are allowable. The claims are not allowable and remain properly rejected under 35 U.S.C. 103 for reasons set forth above and in the previous Office Action.

Applicants have argued at page 20 that the evidence of record clearly shows that the claimed invention is not obvious and should be patentable to the applicant and that the application covers the same invention claimed in the '701 patent. However, contrary to such arguments, the claimed invention is rendered obvious by the combination of references.

Applicants have argued that the sole issue involved is obviousness under 35 U.S.C. 103; that the propriety of the examiner's basis for the rejection is questioned; that ironically, the examiner relies on the very same references relied upon by applicant to show nonobviousness of the claimed

invention. However, contrary to such arguments, applicants have incorrectly assessed the references used; applicants have relied upon only a few of the references cited by the examiner. The examiner agrees with applicant's statement that "the references speak for themselves, and say what they say". Applicants have again argued the teachings of the Liskay declaration and his qualifications as an expert. However, the conclusions of Dr. Liskay have been addressed above.

Applicants have argued that the examiner has totally ignored the facts set forth in the declaration of Dr. Liskay by dismissing it as pure opinion and argue that Dr. Liskay has presented facts of record, or facts he made of record. However, the facts as presented do not support his conclusion as set forth in the declaration and the declaration is therefore not convincing.

Applicant's arguments on page 22-26 are directed to actions to be taken by the Group Director and therefore will not be addressed.

Applicants have argued that the examiner has ignored the facts set forth in the declaration of Dr. Liskay. However, such assertions are incorrect and therefore will address the declaration of Dr. Liskay in detail.

The declarant asserts at paragraph 2 that a particular cell type could be very efficient at performing one type of homologous recombination but relatively incompetent to carry out another type of homologous recombination. However, declarant has provided no evidence to support his assertion and the relevance of the statement to the instant claims is unclear.

The declarant asserts at paragraph 4 that both the '069 and '390 applications involved the targeted integration of a regulatory sequence such as a promoter/enhancer, and/or an amplifiable gene into a mammalian host cell genome to activate

and/or enhance expression of a target gene. However, this assertion is factually incorrect. A reading of the '069 specification does not provide for the targeted integration of a regulatory sequence such as a promoter/enhancer since the application never discloses or suggests the use of a promoter. Further, the '069 application does not suggest or state the use of an amplifiable gene to activate and/or enhance the expression of the target gene since the specification does not disclose or suggest the use of an amplifiable gene to "activate" expression. Declarant has argued that the entire activated gene can be transferred to a secondary expression host cell that is more efficient for large scale production. However, the claims do not claim "large scale production" and therefore declarant's assertions are not commensurate with the scope of the claims. On this issue, declarant's statements are therefore not persuasive.

Regarding paragraph 5, declarant has indicated that both applications describe the use of targeted homologous recombination to integrate a promoter (referred to as the "transcriptional initiation region") into the host genome. Neither application mentions the use of a promoter. They only describe a "transcriptional initiation region" or enhancer. (See page 7 of the specification).

Regarding paragraph 7, declarant has described the invention as being clever and powerful and an approach to gene expression declarant wishes he had thought of himself. This statement contains no facts of science and is clearly opinion. Declarant's further statements as to the advantages over traditional recombinant DNA approaches to gene expression are known in the art and are set forth in the cited references such as Thompson, Smithies and Nandi. Further, declarant's comments directed to the production of the targeted gene product in continuous culture are

not commensurate with the scope of the claims and are therefore not convincing.

Regarding paragraph 8, declarant concludes based upon his review of the '069 grandparent application, and taking into account the knowledge and understanding of one skilled in the art of molecular biology in 1989, that he concludes that the teachings of the '069 grandparent application are not limited to the targeted integration of enhancers, but include the targeted integration of any and all promoter elements different from the wild-type or native promoter that control expression of the target gene. However, declarant's conclusion is an opinion not based on any facts and lacks any explanation of why he so concluded this. The issue remains that the specification ('069) does not disclose use of promoters. It is the examiner's position that in 1989, if one of ordinary skill had intended to claim promoters, than one would have done so at the time the '069 specification was filed since the art (Muller, for example) as well as the ordinary artisan clearly recognized the difference between enhancers and promoters. Declarant has over read the '069 specification and ascribes teachings to the specification not fairly taught.

Regarding paragraph 9, declarant equates the meaning of promoters and transcriptional initiation regions and further states what one of ordinary skill in the art would have thought the phrase "transcriptional initiation region" to mean. These statements by declarant are opinion only since they are his interpretation of the thoughts of others.

Regarding paragraphs 10, 11, declarant discusses the examiner's references concerning the meaning of promoter. Declarant has argued that the "these references also reflect that the transcriptional initiation region as a whole represents the promoter". However, contrary to such assertions, there is no

teaching in the relevant art (Primrose is too old to be relevant) that the transcriptional initiation region as a whole represents the promoter when clearly the relevant reference can distinguish between the transcriptional start site, which is the transcriptional initiation site, and the RNA polymerase binding site. Again although declarant argues that the description and definitions of promoters found in Primrose, Watson and Lewin are consistent with his understanding of the teachings of Dr. Skoultchi's application, the fact remains that the specification does not disclose "promoters" and in view of the state of the art at the time the claimed invention was made, could have been clearly described and claimed. Declarant may not appreciate that a specification must clearly describe and set forth the invention contemplated by the inventor.

Regarding paragraphs 12-17, declarant summarizes certain cited prior art references, not all of which were used as references in a rejection in the previous Office Action, and in paragraphs 18-19 provides his conclusion that the references cited above do not suggest Dr. Skoultchi's invention. However, it is clear from the statements (paragraph 19) that declarant does cannot clearly distinguish between an obviousness rejection and an anticipatory rejection. Declarant's statements "for example, the references do not suggest the targeted recombination of a regulatory sequence such as promoter and/or enhancer, etc." but that the "above identified references do not suggest to one skilled in the art of molecular biology the unique combination of elements or features of Dr. Skoultchi's invention as taught in his patent applications to control the expression of a gene via targeted gene activation" seem to indicate that declarant has expected to find the exact invention in one of the cited references. Further, declarant has argued teachings of references not used in the current 103 rejection and therefore are not

applicable to the rejections at hand. In addition, declarant's comments appear to be directed to the specification and not to the claims since the claims are not drawn to "gene activation".

Regarding paragraph 20, declarant describes the teachings of the Thomas reference, not a primary reference, and declares that the teachings of Thomas are quite the opposite of Dr. Skoultchi's invention which utilizes homologous recombination to activate or enhance target gene expression. However, declarant's comments are again appear to be directed to the specification, not the claims.

Regarding paragraph 21, declarant discusses the teachings of Thompson and Song and declares that neither suggests the use of targeted homologous recombination to activate target gene expression. However, declarant has argued the references individually, not in combination, and secondly, Song is no longer a reference of a rejection. Therefore, declarant's statements are not directed to either the claims or rejections at hand. Note the claims do not claim "activation of target gene expression" but claim "expression of the endogenous target gene is controlled by the integrated regulatory sequence". Control of gene expression may be inactivation as well as activation.

Regarding paragraph 22, declarant states that Thompson does not suggest the wholesale replacement of the control sequence of the target gene with an exogenous control sequence. However, the claims do not claim replacement of the entire regulatory sequence and therefore declarant's statements are not commensurate with the scope of the claims. Declarant also asserts that Thompson does not suggest that recombination could be used to activate gene expression for purposes such as large scale protein production in cell culture. Thompson et al., however, do specifically suggest manipulating the expression of genes by targeting changes to their control sequences for potential commercial value to increase output.

Regarding paragraphs 23 and 24, declarant summarizes the teachings of Liskay and Anderson and discusses the teachings of each separately and not in combination with the references of the current rejection such as Thompson, Smithies and Nandi. Declarant does state that "The ability of a host cell to carry out intrachromosomal homologous recombination did not necessarily suggest anything regarding the capacity of that cell to carry out gene targeting"; however, no reasoning or evidence is provided to support that conclusion. Therefore, the statement constitutes opinion. Regarding the teachings of Anderson and the "formidable task", it has been previously discussed that "formidable" does not mean "not possible" and secondly, Anderson was not cited to teach the use of homologous recombination to activate target gene expression. Further, the claims do not claim "activation of target gene expression" and therefore declarant's statements are not commensurate with the scope of the claims.

Regarding paragraph 25, declarant declares that "Based on the teachings, experiments, and data described in the foregoing references, and taking into account the knowledge that one of ordinary skill in the art of molecular biology would have had in 1989, I have come to the conclusion that the references would not have provided such a person with a reasonable expectation of successfully activating gene expression using targeted homologous recombination in mammalian cells". However, declarant's conclusion is opinion since declarant cites no specific teachings, evidence or data anywhere in any of the references which teach away from a reasonable expectation of success. Again, the claims do not claim "activating gene expression", merely that expression is controlled by the integrated regulatory sequence, and as set forth above, control of expression may also be inhibition or downregulation as well as activation of that expression and Thompson specifically suggests such manipulation.

Regarding paragraph 26, declarant attests to the state of the art in 1989 with respect to homologous recombination and that at the time targeted homologous recombination was known to occur efficiently in lower organisms such as bacteria and yeast and that targeted homologous recombination was in general viewed as a rare event and difficult task in most commonly used mammalian cells. However, declarant has not provided references, data or other evidence to support such assertions. Indeed, the examiner can refute declarant's assertion of homologous recombination as a rare and difficult task in Smithies wherein it is stated (page 230, column 1, second full paragraph) "Although the frequency of success (~10^{-3} of the transformed cells) is at present modest, the data show unequivocally that the planned modification of a specific human gene is possible in vivo". Neither declarant nor applicant has provided evidence to support their conclusions of no reasonable expectation of success. Further, declarant's statement that homologous recombination was viewed as a difficult task is unsupported and contrary to the evidence provided by the examiner. While homologous recombination may in fact be a rare event in terms of absolute numbers, homologous recombination has been shown by the references above and of record to occur in mammalian cells as an expected event. Further, cells are cultured collectively in the millions, not individually, and therefore within in any cell culture in a homologous recombination experiment, some cells will have undergone homologous recombination. In addition, the claims do not claim any degree of efficiency of homologous recombination and therefore declarant's statements are not commensurate with the scope of the claims. Declarant has further interpreted the teachings of Anderson as teaching away from the use of homologous recombination in mammalian cells, characterizing it as a formidable task. Contrary to declarant's assertions, Anderson states that homologous site

specific integration occurs at a very low level, when it occurs at all, in mammals. Anderson does not teach away since Anderson does state that homologous recombination does occur in mammalian cells, that it is a rare event in the statement "when it occurs at all" and does not teach away since the claims do not claim any degree of efficiency of homologous recombination.

Regarding paragraph 27, declarant states that the prevailing view held at the time was that ES cells were somehow special, in that these embryonic cells might possess unique capabilities to perform targeted homologous recombination more efficiently than other cells; that the ES cell system was viewed as more similar to bacterial and yeast systems which were thought to be efficient at targeted homologous recombination; and that results obtained in the mouse ES system were not generally extended, extrapolated or considered predictive of results that could be achieved in other mammalian cells. However, contrary to such arguments, the claims claim a mammalian host cell, which includes ES cells, and do not claim any particular efficiency of homologous recombination. Further, declarant has not provided evidence supporting his assertions of that ES cells were special, viewed more similar to bacterial and yeast systems and that the ES cell results were generally not extended, extrapolated or considered predictive.

Regarding paragraph 28, declarant has argued the teachings of Song and that attempts to target mutations into endogenous native genes were not as successful as the results achieved for Song's artificial targets and that declarant knows of only one report (Smithies, of record) relating to gene targeting for modifying or correcting endogenous genes in mammalian cells and that the results were modest. However, contrary to such arguments, the claims claim no degree of efficiency of homologous recombination and therefore the modest results achieved meet the

claim limitations. Declarant's arguments are not commensurate with the scope of the claims. Moreover, although Smithies et al. do indicate a "modest" frequency of success,they state that "the data show unequivocally that the ....modification...is possible in vivo". Such a statement must be interpreted as a success and providing a reasonable expectation of success despite Dr. Liskay's statement to the contrary. Such statement is positive not negative about success.

Further, declarant's further discussion of the Song results and statement that the Song experiments would not have provided one of ordinary skill with a reasonable expectation of successfully targeting native endogenous genes in mammalian host cells is not directed to any rejection outstanding, argues a reference individually and is not commensurate with the scope of the claims.

Regarding paragraph 29, declarant argues the teachings of the Liskay reference; however, Liskay has been withdrawn as a reference and declarant's arguments are therefore moot.

Regarding paragraph 30, declarant states that Dr. Skoultchi's invention represents a unique and unusual approach to gene expression; that although each of the tools utilized in the invention were known individually such as promoters, enhancers, gene targeting, amplifiable genes the unique combination of the various elements had not been suggested, i.e., that the use of gene targeting to engineer exogenous promoter/enhancers and/or amplifiable genes into mammalian host cells so that expression of endogenous target genes is controlled, activation or enhanced by the exogenous integrated sequences and that none of the references suggested the use of targeted recombination for combined gene activation and amplification. However, contrary to such assertions, the cited prior art renders obvious the claimed

invention since the cited references provide both the motivation and a reasonable expectation of success.

In conclusion, the declaration is not convincing of unobviousness since declarant has not provided factual evidence to support the numerous arguments asserted above regarding the conclusions of non-obviousness and no reasonable expectation of success.

The following new grounds of rejection are applicable to the newly entered claim, claim no. 105.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description and for failing to adequately teach how to make and/or use the invention as claimed,i.e., failing to provide an enabling disclosure. The specification fails to disclose how to express a gene product encoded by a normally transcriptionally silent target gene. Both embodiments in the specification deal with cell lines which constitutively express the target gene. In the first embodiment, the specification discloses integration of the CMV enhancer/promoter via homologous recombination upstream of, and in operable linkage to, the EPO gene in human embryonic kidney cells which are known in the art to constitutively express EPO. Therefore, this particular embodiment does not teach or demonstrate how to express a gene product encoded by a normally

transcriptionally silent target gene. The second embodiment deals with a construct comprising the 1.45 kb of DNA flanking the transcriptional start of human tPA in addition to the first exon and part of the first intron, which is then put into the plasmid pUCD to generate a plasmid pUCG which then contains the promoter of the tPA fragment in opposite orientation to the DHFR cassette. After linearization, the construct is transformed into primary human diploid fibroblasts. Human primary diploid fibroblasts are known in the art to constitutively express tPA.Therefore, this particular embodiment does not teach or demonstrate how to express a gene product encoded by a normally transcriptionally silent target gene. In addition, this embodiment apparently replaces part of the endogenous gene with a construct having 1.45 kb of DNA containing the wild-type tPA promoter, first exon and part of the first intron, considerably more than a "heterologous regulatory sequence" as claimed in claim 105. There is no evidence in the specification that either embodiment is an example of the situation wherein the "target gene is normally transcriptionally silent". In this latter case wherein the gene is normally transcriptionally silent, transcriptional silence of genes is known in the art to be due to a wide variety of factors, such as gene silencers, mutations in coding regions or regulatory regions of genes or lack of transactivating factors needed to induce transcription. The specification fails to identify those particular genes wherein the "gene is normally transcriptionally silent" and to teach one of ordinary skill methods to overcome transcriptional silence in those instances. Case law teaches (Ex parte Forman, 230 USPQ 546, 547 (PTO Bd. App. Int. 1986)that "the disclosure of a patent application must enable practice of the invention claimed without undue experimentation", wherein factors involved in the determination of undue experimentation were deemed to include "the quantity of experimentation necessary, the

amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims". In view of the lack of direction or guidance in the specification regarding which genes are transcriptionally silent and methods of overcoming the transcriptional silence, it would require undue experimentation by one of ordinary skill to determine why a particular gene is transcriptionally silent and to determine the method to overcome the silence. One of ordinary skill would be required to obtain the genomic nucleotide sequence of the gene as well as the nucleotide sequence of large stretches of 5' and 3' flanking sequences in order to determine, if possible, the presence or absence of positive or negative regulatory sequences, mutations such as point mutations, insertions or deletions, influencing gene transcription. It is known in the art of immunoglobulin gene structure, for example, that the 3' enhancer for the kappa chain occurs approximately 9kb downstream of the last exon and further that the 3' enhancer is required for gene expression. The state of the art at the time the claimed invention was made was that regulatory elements influencing gene transcription were known to exist upstream, downstream, within introns, close to or far removed from the actual coding sequence. It would require undue experimentation by one of ordinary skill to determine the nucleotide sequence of literally tens of thousands of base pairs upstream and downstream of the gene of interest in order to determine the presence or absence of silencer elements or enhancers, if known, for example, or to identify unknown elements based on nucleotide sequence identity with known analogous counterparts. Thus, the basis for a normally transcriptionally silent target gene was unpredictable and the specification provides no guidance for determining which

genes could be expressed simply upon insertion of a heterologous promoter via homologous recombination.

The specification fails to adequately teach how to make or use the invention as claimed without undue experimentation since the specification fails to provide guidance as to which genes would be expected to be transcriptionally active upon insertion of a heterologous promoter via homologous recombination. Further, in view of the lack of working examples demonstrating overcoming transcriptional silence by insertion of a regulatory sequence by homologous recombination, in view of the art recognized basis for gene silence, and in view of the breadth of the claim claiming any transcriptionally silent gene, it would require undue experimentation by one of ordinary skill to make or use the invention as claimed.

In addition, the specification fails to provide support for the claim language of claim 105. The specification discloses that "the gene of interest may or may not be expressed" and does not provide either literal or inherent support for the phrase "normally transcriptionally silent target gene". It is known in the art that gene expression involves protein production and therefore both transcription and translation. When the "gene of interest may or may not be expressed" the problem may be related to the translational process and unrelated to transcriptional silence. Therefore, in view of the multiple reasons for lack of gene expression, one of ordinary skill does not immediately envision "transcriptional silence" from the phrase "the gene of interest may or may not be expressed". It is well known in the art that after the transcription has occured, the RNA thus produced undergoes processing. The RNA may have a short half-life or be degraded or simply not be translated, all of which result in a lack of protein production. Indeed, it is well known in the art that some immunoglobulin genes are transcribed but not

translated (pseudogenes)since they are not correctly spliced. Therefore, transcriptional silence, which is lack of transcription, entails different problems and may be unrelated to lack of protein production from a target gene.

Claim 105 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim 105 is rejected under 35 U.S.C. § 102(e) as being anticipated by Chappel (U.S. P.N. 5,272,071). Chappel discloses that normally transcriptionally silent genes in a cell line or microorganism may be activated for expression by inserting a DNA regulatory element, the regulatory element being inserted so as to be operatively linked with the normally silent gene. See column 4, lines 58-68. Therefore, the reference anticipates the claims.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Suzanne Ziska, Ph.D., whose telephone number is (703)308-1217. In the event the examiner is not available, the examiner's

supervisor, Ms. Jacqueline Stone, may be contacted at phone number (703) 308-3153.

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